

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203985Orig1s000**

**CHEMISTRY REVIEW(S)**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** August 24, 2012  
**FROM:** Sue-Ching Lin, CMC Reviewer  
**TO:** **NDA 203985**  
**SUBJECT:** Final CMC recommendation for NDA 203985

NDA 203985 was initially submitted on 29-Feb-2012 and was granted a priority review by the Agency. Chemistry Review #1 (02-Aug-2012) resulted in a recommendation for approval pending a determination of acceptability from ONDQA biopharmaceutics reviewer and pending the receipt of an overall acceptable recommendation from the Office of Compliance. At the time of CMC review finalization, the biopharmaceutics review and overall compliance recommendation were still pending.

This memo serves to update that determination. The biopharmaceutics reviewer (Dr. Kareen Riviere) issued a recommendation for approval in a review dated 03-Aug-2012. An overall acceptable recommendation was issued by the Office of Compliance on 23-Aug-2012.

All CMC deficiencies have been resolved, and there are no outstanding issues with this NDA. Therefore, approval of NDA 203985 is recommended from a CMC perspective. Please note that the applicant has agreed to fulfill two post-marketing commitments as documented in the CMC and biopharmaceutics reviews.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SUE CHING LIN  
08/24/2012

NALLAPERUM CHIDAMBARAM  
08/24/2012  
I concur

**NDA 203985**

**Afinitor<sup>®</sup> Disperz<sup>™</sup>**  
**(everolimus tablets for oral suspension)**

**Novartis Pharmaceuticals Corporation**

**Sue-Ching Lin**

**Review Chemist**

**Office of New Drug Quality Assessment**  
**Division of New Drug Quality Assessment I**  
**Branch II**

**CMC REVIEW OF NDA 203985**  
**For the Division of Oncology Products 2**

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CMC Review Data Sheet

# CMC Review Data Sheet

1. NDA 203985
2. REVIEW #: 1
3. REVIEW DATE: 02-Aug-2012
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 22-334 CMC review for Drug Substance sections	05-Mar-2009
NDA 22-334 CMC review for Drug Product sections	18-Mar-2009
NDA 22-334 CMC review (for widening of the limit for impurity (b) (4))	02-Nov-2010
NDA 22-334/S-011 CMC review (for addition of 7.5 mg tablets)	26-Jul-2011
NDA 22-334/S-012 CMC review (updated drug product specification)	05-Oct-2012
IND 66,279 27-Sep-2011 pre-NDA meeting minutes	11-Oct-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	DARRTS SD Number	Document Date	Stamp Date
Original NDA Submission	1	29-Feb-2012	29-Feb-2012
Amendment (Response to FDA 4/9/12 CMC IR)	4	12-Apr-2012	12-Apr-2012
Amendment (Response to biopharm 3/19/12 IR about dissolution issues)	6	16-Apr-2012	16-Apr-2012
Amendment (History of labeling changes)	11	15-May-2012	15-May-2012
Amendment (Response to FDA 5/11/12 Filing Issues)	12	29-May-2012	29-May-2012
Amendment (Response to FDA 6/1/12 IR regarding physician sample labeling, oral syringe preparation issues, etc.)	13	08-Jun-2012	08-Jun-2012
Amendment (Response to 7/5/12 CMC IR)	16	13-Jul-2012	13-Jul-2012
Amendment (Response to biopharm 6/20/12 IR)	17	19-Jul-2012	19-Jul-2012
Amendment (Response to 7/19/12 CMC IR regarding container, stability commitment, and method validation )	21	25-Jul-2012	25-Jul-2012
Amendment (Response to e-CTD format change for Module 3)	23	26-Jul-2012	26-Jul-2012

## CMC Review Data Sheet

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation  
Address: One Health Plaza  
East Hanover, New Jersey 07936-1080  
Representative: Yanina Gutman, PharmD, Associate Director  
Telephone: (862) 778-1767

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Afinitor<sup>®</sup> Disperz<sup>™</sup>  
b) Non-Proprietary Name: everolimus tablets for oral suspension  
c) Code Name/# (ONDQA only): RAD001  
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: Type 3 (new dosage form)
  - Submission Priority: Priority

## 9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

## 10. PHARMACOL. CATEGORY: antineoplastic agent (inhibitor of mTOR)

## 11. DOSAGE FORM: tablets for oral suspension

## 12. STRENGTH/POTENCY: 2 mg, 3 mg, 5 mg

## 13. ROUTE OF ADMINISTRATION:

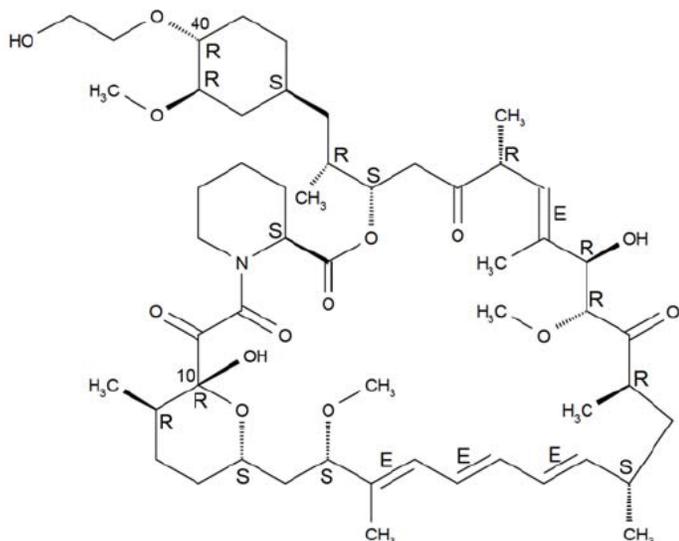
14. Rx/OTC DISPENSED:  Rx  OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

## CMC Review Data Sheet

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular formula:  $C_{53}H_{83}NO_{14}$   
Relative molecular mass: 958.2

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	7	N/A	N/A	Refer to information in NDA 22-334
	III			3 & 4	adequate	07-Mar-2008	See Section 3.2.P.7
	III			4	N/A	N/A	See Section 3.2.P.7

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

CMC Review Data Sheet

- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	66,279	RAD001
NDA	22-334 original NDA dated 6/30/08	Afinitor Tablets, CMC information to support 5 mg and 10 mg tablets
NDA supplement	22-334, 12/22/09 supplement (Supplement S-05, DARRTS SD-68)	CMC information to support 2.5 mg tablet strength
NDA supplement	22-334, 3/29/11 supplement (Supplement S-11, DARRTS SD-139)	CMC information to support 7.5 mg tablet strength

18. STATUS:

**ONDQA:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending	Pending	Pending
Pharm/Tox	N/A		
Biopharm	Pending	Pending	Kareen Riviere
LNC*	The dosage form is “tablets for oral suspension” instead of the proposed (b) (4)	06-Apr-2012	Dr. Richard Lostritto, LNC Chair, and Ms. Yana Mille of LNC Committee provided LNC recommendation via e-mails.
Methods Validation	N/A, according to the current ONDQA policy in IQP 5105		
DMEPA**	The proposed proprietary name “Afinitor Disperz” is acceptable.	31-May-2012	James H. Schlick
EA	Categorical exclusion (see review)	Date of this review	Sue-Ching Lin
Microbiology	Recommended approval	22-Mar-2012	Steven P. Donald

\*LNC: Labeling and Nomenclature Committee

\*\*DMEPA: Division of Medication Error Prevention and Analysis

## Executive Summary Section

# The CMC Review for NDA 203985

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the perspective of chemistry, manufacturing, and controls, this NDA may be approved, pending an “acceptable” overall recommendation from the Office of Compliance for the inspections of the manufacturing and testing facilities for the drug substance and drug product and an approval recommendation from ONDQA biopharmaceutics reviewer (review pending).

Based on the provided stability data, an 18-month expiration dating period is granted for the drug product when stored at the proposed controlled room temperature and protected from light and moisture. The expiration dating period can be extended to 24 months upon fulfillment of the post-marketing commitment (PMC) as described below.

Include the following statement in the action letter:

An expiration dating period of 18 months is granted for the drug product, when stored at 25°C (77°F) excursions permitted between 15°C to 30°C (59°F to 86°F), protected from light and moisture.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Novartis has agreed to fulfill the post-marketing commitment (PMC) within the specified timeline as follows:

*Novartis will conduct pre-validation as well as validation activities for the blistering process for the container closure system that will be used for the US market. The USP <671> Water Vapor Transmission Rate test (WVTR) will be performed with blister cards derived from Pre-Validation trials. The most stringent requirement, Class A <0.5 mg/day, will need to be met before proceeding with validation and launch activities.*

*To bridge the registration stability and the launch batches Novartis will ensure that the WVTR result is comparable to that measured for the registration stability batches.*

(b) (4)  
(b) (4) *an acceptable WVTR result in combination with successful pre-validation and validation on the packaging process will provide assurance that the registration stability data is bridged to the intended commercial product. Novartis will provide the comparable USP<671> WVTR data before the end of November 2012.*

## Executive Summary Section

Novartis also commits to submitting the <sup>(b)</sup><sub>(4)</sub> months accelerated stability data on the first <sup>(b)</sup><sub>(4)</sub> commercial batches before the end of May 2013.

## II. Summary of CMC Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

#### (1) Drug Substance

The drug substance, everolimus, is a macrolide derived from <sup>(b)</sup><sub>(4)</sub> by <sup>(b)</sup><sub>(4)</sub> <sup>(b)</sup><sub>(4)</sub>, also known as <sup>(b)</sup><sub>(4)</sub>, is a <sup>(b)</sup><sub>(4)</sub> product.

The drug substance everolimus is a white to faintly yellow powder. The drug substance is practically insoluble in water but is soluble in organic solvents. It is very susceptible to oxidation and is sensitive to light. Because of the <sup>(b)</sup><sub>(4)</sub> <sup>(b)</sup><sub>(4)</sub> everolimus is <sup>(b)</sup><sub>(4)</sub>

Detailed information on the drug substance is referenced to the applicant's approved NDA 22-334 for Afinitor (everolimus) Tablets.

#### (2) Drug Product

The drug product, Afinitor Disperz, will be supplied as 2 mg, 3 mg and 5 mg tablets for oral suspension. It was developed to disintegrate more rapidly than Afinitor Tablets (NDA 22-334) and thus ensures a fast and simple preparation of the oral suspension.

As with the manufacture of Afinitor Tablets in NDA 22-334, the drug substance is <sup>(b)</sup><sub>(4)</sub>

The outer phase of the tablet contains <sup>(b)</sup><sub>(4)</sub>. In comparison with Afinitor Tablets, the outer phase of this drug product has been developed to minimize disintegration time and to quickly release the fine particles of the solid dispersion within 3 minutes.

¶

## Executive Summary Section

All dosage strengths are manufactured from the [REDACTED] (b) (4)

**B. Description of How the Drug Product is Intended to be Used**

Everolimus is an antineoplastic agent. It is an inhibitor of mammalian target of rapamycin (mTOR), a serine-threonine kinase. The drug product Afinitor Disperz (everolimus tablets for oral suspension) is indicated for the treatment of patients with subependymal giant cell astrocytoma (SEGA) and tuberous sclerosis complex (TSC) in conjunction with therapeutic drug monitoring.

The recommended starting dose is 4.5 mg/m<sup>2</sup>, once daily. Conduct therapeutic drug monitoring to achieve and maintain trough concentrations of 5 to 15 ng/mL. Adjust dose at two week intervals, as needed.

**C. Basis for Approvability or Not-Approval Recommendation**

The CMC information of the drug substance was referenced to the applicant's approved NDA 22-334 for Afinitor (everolimus) Tablets.

Adequate data have been provided to ensure the quality of the drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Afinitor Disperz. Per FDA request, the dosage form was revised from [REDACTED] (b) (4) which was proposed in the original NDA submission, to "tablets for oral suspension," as the term [REDACTED] (b) (4) is not an acceptable dosage form term recognized by the Agency.

The CMC revisions of the package insert have been incorporated into the revised labeling during the labeling meetings of the NDA. In addition, issues related to container labels and carton labeling have been adequately resolved. During the labeling meetings, the Division determined that the presentation of the proprietary name and nonproprietary name should be Afinitor Disperz (everolimus tablets for oral suspension), because the proprietary name Afinitor Disperz is for a specific dosage form (tablets for oral suspension) and thus the dosage form should be displayed within the parentheses.

The Office of Compliance has not issued an overall recommendation for the inspections of the manufacturing and testing facilities for the drug substance and drug product. Therefore, this NDA may not be approved until a final acceptable recommendation is made by the Office of Compliance.

## Executive Summary Section

As shown in Section IB of this Executive Summary, the applicant has agreed to fulfill the Post-marketing Commitment (PMC), if an approval is recommended for this NDA. Note that the biopharm reviewer also requested a PMC for dissolution method.

**III. Administrative****A. Reviewer's Signature:**

*(See appended electronic signature page)*

Sue-Ching Lin, M.S., R.Ph., Reviewer, ONDQA

**B. Endorsement Block:**

*(See appended electronic signature page)*

Nallaperum Chidambaram, Ph.D., Acting Branch Chief, Branch II, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

**C. CC Block:** entered electronically in DARRTS

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/s/  
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SUE CHING LIN  
08/02/2012

JANICE T BROWN  
08/02/2012  
Janice Brown for Nallaperum Chidambaram

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)**

**NDA Number:**  
203-985

**Supplement Number and Type:**

**Established/Proper Name:**  
everolimus

**Applicant:** Novartis  
Pharmaceutical  
Corporation.

**Letter Date:** 29 February, 2012  
(Resubmission)

**Stamp Date:**  
29 February, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	Yes		Reference to approved Afinitor NDA22-334
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			pre-NDA meeting is held on 27-Sep-2011.

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			N/A

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	Yes		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	Yes		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	Yes		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Yes		

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	Yes		

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	Yes		Reference to approved Afinitor NDA22-334
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	Yes		Reference to approved Afinitor NDA22-334
14.	Does the section contain information regarding the characterization of the DS?	Yes		Reference to approved Afinitor NDA22-334
15.	Does the section contain controls for the DS?	Yes		Reference to approved Afinitor NDA22-334
16.	Has stability data and analysis been provided for the drug substance?	Yes		Reference to approved Afinitor NDA22-334
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		No	See Dr. Debasis Ghosh's e-mail
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		No	See Dr. Debasis Ghosh's e-mail

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Yes		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	Yes		
21.	Is there a batch production record and a proposed master batch record?	Yes		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Yes		In drug development section and reference to approved NDA
23.	Have any biowaivers been requested?			Fileable from Biopharm. See biopharm filing review in DARRTS. Also IR is issued.
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	Yes		
25.	Does the section contain controls of the final drug product?	Yes		
26.	Has stability data and analysis been provided to support the requested expiration date?			Review issue
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		No	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	Yes		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	Yes		Tablet for solution

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	Yes		LoA provided

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA PROVIDED?	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	Yes	
(b) (4)	III	(b) (4)	(b) (4)	Yes	

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	Yes		Dosage name needs to be evaluated Afinitor (b) (4) vs Afinitor tablets for solution or suspension
33.	Have the immediate container and carton labels been provided?	Yes		

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW and IQA FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	Yes		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.	Yes		No CMC fileability issue.
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?		No	Afinitor (b)(4) vs Afinitor tablets for solution or suspension.

Note: RAD001 2 mg, 3 mg and 5 mg dispersible tablets contain everolimus [40-O-(2-hydroxyethyl)- rapamycin] as the active drug substance. The drug substance is alternatively known as RAD001 or RAD001 (b)(4), which is (b)(4) for commercially available Afinitor® immediate release tablets. Everolimus has been formulated as 2 mg, 3 mg and 5 mg dispersible tablets for oral administration for the treatment of patients with TSC who have subependymal giant cell astrocytoma (SEGA) not requiring immediate surgery. There are several potential concerns as follows:

- The proposed dosage name needs to be evaluated, for example: Afinitor (b)(4) vs Afinitor tablets for solution or suspension.
- Appropriate dissolution method needs to be reviewed by ONDQA Biopharm team
- Total impurities and individual impurity acceptance criteria should be evaluated

Liang Zhou

3-27-2012

Name of  
 CMC Lead / CMC Reviewer  
 Division of Pre-Marketing Assessment # 1  
 Office of New Drug Quality Assessment

Date

{Sarah Pope Miksinski}

3-27-2012

Name of  
 Branch Chief  
 Division of Pre-Marketing Assessment # 1  
 Office of New Drug Quality Assessment

Date

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/s/  
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LIANG ZHOU  
03/27/2012  
Filing Review and IQA

HARIPADA SARKER  
03/27/2012